Synthesis, Characterization and Anti Microbial Activity of Some New Derivatives Containing Imidazol Moiety

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الخلاصة

يتضمن هذا البحث تحضير بعض مشتقات الايميدازول الجديدة وذالك بتفاعل 4- نايترو انيلين مع 3- كلورو-2 , 4 بنتادايون بوجود بوتاسيوم ثايوسيانيد ليعطي [(1-4 نايتروفنيل)-2- مركبتو-4-مثيل -H1 –اميدازول-5-يل)] ايثانون(1). الذي يتفاعل مع الديهايدات اروماتية مختلفة حسب تكاثف claisen. Schmidt لنحصل على الجالكونات (4a-c) التي يتفاعل مع الهيدرازين هيدريت لنحصل على مشتقات البايروزول(3a-c). اما مشتقات (4a-c) فتحضر من معاملة مشتقات البايروزول مع بنزويل كلورايد بوجود تراي مثل امين. الجالكونات تدخل تفاعل غلق حلقي مع الهيدروكسيل امين هايدروكلورايد لتعطي مشتقات ايزواوكسازول (5a-c) التي تتفاعل مع فيوران -2- الديهايد للحصول على المركبات (6a-c).

كل المركبات تم تشخيصها باستخدام تقنية FTIR و ^{1}H-NMR كما تم دراسة فعاليتها البايولوجية(Anti microbial) باستخدام طريقة (cup plate agar diffusion)

Abstract

This paper involves synthesis some new imidazol derivatives were synthesized reaction of p-nitro Aniline with 3-chloro 2,4-pentadione with KSCN to give [1-(4-Nitro Phenyl)-2-Mercapto-4-methyl-1H-imidazol-5-yl)]-ethanone(1). Which reaction with different aromatic aldehydes according to claisen. Schmidt condensation to get a chalcones were reacted with hydrazine Hydrate to obtained the pyrazol derivatives and (4a-c) was synthesized by the treatment of pyrazol derivatives with benzoyl chloride in TEA. The chalcones were cyclized with the hydroxyl amine hydro chloride to give an iso oxazole derivatives which condensed with furan-2-aldehyde to obtain compounds(6a-c). These compounds were characterized using FTIR and ^{1}H-NMR. Anti microbial study in vitro screened against several bacterial by cup plate agar diffusion method and also very good antibacterial activity was observed.

Keywords: *imidazol 2-thiol, chalcones, pyrazoles, 1,2 oxazol, Antimicrobial activity.*

Introduction

Imidazol-2-thiol derivatives that contains carbon bonded sulfyl(-C-SH) group plays a very wide and important role in biological activity like anti bacterial[1], anti fungal[2], anti flammatory[3], sympathominetic activity[4] and anti retrovirus Activity such as human immumodeficiency syndromes[5]. Anti bacterial activates the azoles are the widely spectrum and in clinical practice as anti microbial agents. Pyrazole is an important of heterocyclic compounds such as herbicidal[6], antitumor, molecular modeling, cytotoxic[7], and antiviral[8], pyrazole derivatives also acts as kinase inhibitor for treatment of type -2 diabetes, obesity, hyper lipidemia[9], and thrombopiotinmimetics[10]. Iso oxazole have been reported from numerous marine organisms[11]. They have various biological activities including anti fungal activity[12] cytotoxic[13], They synthesis of imidazole-2-thiol derivatives and illustrate their activities against some gram negative and gram positive bacterial as well as Candida fungal. To explain the promising activity of these derivatives.

Experimental part

Synthesis

All solvent and starting material were purchased from fluska and Aldrich. ^{1}H-NMR spectra were obtained with Burker spectrophometer model Ultra shield at 300 MHZ in DMSO –d6 solution with the TMS as internal standard. Melting point of the synthesized compounds were determined in open capillary tubes and has been found uncorrected FT-IR measurements were recorded on a shimadzu model FTIR -84005.

Synthesis of 1-[1-(4-nitro phenyl)-2-mercapto-4-methyl-1H-imidazol-5-yl]-ethanone(1)[14]:

3-chloro-2,4-pentanedione(0.02mol) was added as a drop wise to solution of 4-nitro aniline(0.02mole) in ethanol (20ml) with stirring for 1h at 0-5^{o}c. then, after that the stirred for 2 hrs at room temperature reaction mixture was kept for 12 hrs, and then was added to the mixture (0.02mole) potassium thiocynate which was heated under reflux for 4 hrs, cooled,

poured into ice water. The solid product was filtered , washed with distilled water and recrystallized from ethanol.

IR-(KBr,cm^{-1}): 1666(C=O), 1539(C=N), 1595-1475(C=C), 3037(aromatic-CH), ^{1}H-NMR δ ppm: 2.7(s,3H,COCH3); 2.3(s,3H,CH3), 12(s,1H.SH), 7.6-8.4(m,4H,Ar-H)

Procedure for the synthesis of the chalcones (2a-c)[15]

The compound 1 (1mole) was reacted with substituted aromatic aldehyde (1mole) in ethanol (30 ml) with constant stirring at room temperature. And then add to reaction mixture (2%) KOH solution with stirring for 24 hrs and kept for 24 hrs. at room temperature. The precipitates so obtained were filtered, washed with water, dried and purified by re crystallization (H_2O and ethanol)1:1 to get the desired products.

2a: 1-[2-mercapto-4-methy)-1-(4-nitro phenyl)-1H-imidazol-5-yl)-3-(4-hydroxy phenyl)-prop-2-en-1-one : IR(KBr,cm^{-1}): 1502(C=CH), 1653(C=O); ^{1}H-NMR δ (ppm): 3.4(s,3H,Ar-CH_3),7.7-8.8(m,8H,Ar-H), 10.5(s,1H,OH), 7.5-7.8(d,1H, Ar-CH=)

2b: 1-[2-mercapto-4-methy)-1-(4-nitro phenyl)-1H-imidazol-5-yl)-3-(4-chloro phenyl)-prop-2-en-1-one: IR(KBr,cm^{-1}):1640(C=O),1490(C=CH); ^{1}H-NMRδ (ppm):2.9(s,3H,Ar-CH_3),6.8-7.4(m,8H,Ar-H), 7.2-7.6(d,1H, Ar-CH=)

2c: 1-[2-mercapto-4-methy)-1-(4-nitro phenyl)-1H-imidazol-5-yl)-3-(4-bromo phenyl)-prop-2-en-1-one: IR(KBr,cm^{-1}):1645(C=O),1492(C=CH), 3055(aromatic C-H), 2166(-SH); ^{1}H-NMR **δ** (ppm):2.7(s,3H,Ar-CH_3), 7.3-7.6(d,1H, Ar-CH=)7.2-8.3(m,8H,Ar-H)

General procedure for the synthesis of the pyrazole derivatives[16]:

A mixture of hydrazine hydrate(0.025 mol) and 1-[2-mercapto-4-methy)-1-(4-nitro phenyl)-1H-imidazol-5-yl)-3-(4-subsitituted phenyl)-prop-2-en-1-one(0.025 mol) in ethanol(20ml) was heated under reflux for 8-10 hrs. after that, the excess of solvent was distilled off, poured on to crush ice , the products solid was filtered, washed with distilled water and recrystallized from methanol.

3a: 5-[5-(4-hydroxy phenyl)-5,4 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}):1590(C=N), 3062(aromatic C-H), 3310(N-H), 1514 (C=C); ^{1}H-NMR δ (ppm): 2.3(s,3H,Ar-CH_3), 9.5(s,1H, NH-pyraz), 4.2-4.0(dd,1H,-CH_2pyraz), 7.3-8.1(m,8H,Ar-H),4.5 (dd,1H,-CHpyraz).

3b: 5-[5-(4-chloro phenyl)-5,4 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}):1600(C=N), 3212(N-H), 1520(C=C), 3053(aromatic C-H); ^{1}H-NMR δ (ppm):2.5(s,3H,Ar-CH_3), 10.1(s,1H, NH-pyraz), 4.1-4.4(dd,1H,-CH_2pyraz) 7.4-8.6(m,8H,Ar-H),4.6 (dd,1H,-CHpyraz)

3c: 5-[5-(4-bromo phenyl)-5,4 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}):1604(C=N), 3304(N-H), 1530(C=C), 3092(aromatic C-H); ^{1}H-NMR δ (ppm): 2.3(s,3H,Ar-CH_3), 9.1(s,1H, NH-pyraz)

4.2-4.5(dd,1H,-CH_2pyraz), 7.2-8.4(m,8H,Ar-H),4.8 (dd,1H,-CHpyraz)

Procedure for the synthesis of (4a-c) derivative[17]

(0.01mol) of benzyl chloride was added drop wise to ice cold mixture of (3a-c) derivatives(0.01mol) and then dissolved in tri ethyl amine(30ml) with constant stirring at (0-5)^{0}C. after that , the stirred was used for 1hr at room temperature for reaction mixture. Then the products was poured over ice water and neutralized with HCL, the precipitate was the filtered, washed with distilled water and recrystallized from methanol.

4a: 5-[1-(phenyl)-methane one-5-(4-hydroxy phenyl))-4,5 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitrophenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}):1623(C=O), 3072(aromatic C-H), 1601(C=N), 1520(C=C), 3301(Ar-OH); ^{1}H-NMR δ (ppm): 2.5(s,3H,Ar-CH_3), 4.9 (dd,1H,-CHpyraz) ,3.2-3.0 (dd,1H,-CH_2pyraz) 7.4-8.2(m,13H,Ar-H)

4b: 5-[1-(phenyl)-methane one-5-(4-chloro phenyl))-4,5 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitrophenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}):1635(C=O), 1605(C=N), 1518(C=C), 3043 (aromatic C-H);^{1}H-NMR δ (ppm): 5.1 (dd,1H,-CH2-pyraz), 2.3(s,3H,Ar-CH_3), 7.4-8.0(m,13H,Ar-H)

4c: 5-[1-(phenyl)-methane one-5-(4-bromo phenyl))-4,5 dihydro-1H-pyrazol-3-yl]-4-methyl-1-(4-nitrophenyl)-1H-imidazole-2-thiol: IR(KBr,cm^{-1}): 3066 (aromatic C-H), 1640(C=O), 1607(C=N), 1523(C=C)

General procedure for the synthesis of the compounds (5a-c)[18]

A mixture of derivatives(5a-c) (0.01mole) in ethanol(20ml) hydroxyl amine hydrochloride(0.01mol) and drops of HCL. The mixture was refluxed for 1 hr., after that the reaction mixture was cooled, the resulting solid product was separated and recrystallized from ethanol.

5a-: 5-[5-(4-hydroxy phenyl)-4,5 dihydro-1,2-oxazol 3-4yl]-4-methyl-1-(4-nitro phenyl)-1H- imidazol-2-thiol: IR(KBr,cm^{-1}): 3063(aromatic C-H), 1551(C=C), 1612(C=N), 33100(OH-Ar); ^{1}H-NMR δ (ppm): 1.4 (s,3H, CH_3), 4.2 (dd,2H,-CH2-pyraz), 6.7-7.9(m,8H,Ar-H), 10.7 (s,1H, OH-Ar)

5b-: 5-[5-(4-chloro phenyl)-4,5 dihydro-1,2-oxazol 3-4yl]-4-methyl-1-(4-nitro phenyl)-1H- imidazol-2-thiol: IR(KBr,cm^{-1}): 3098(aromatic C-H),2987(aliphatic C-H),1632(C=N),1524(C=C).

^{1}H-NMR δ (ppm): 1.9 (s,3H, CH_3), 6.6-7.9(m,8H,Ar-H), 5.2 (dd, H,-CH-pyraz), 4.1 (dd,2H,-CH2-pyraz)

5c-: 5-[5-(4-bromo phenyl)-4,5 dihydro-1,2-oxazol 3-4yl]-4-methyl-1-(4-nitro phenyl)-1H- imidazol-2-thiol: IR(KBr,cm^{-1}): 3075(aromatic C-H), 1541(C=C), 1630(C=N), 2982(Aliphatic-CH)

General procedure for the synthesis of (6a-c) derivatives[19]:

Eguimolar solution of (5a-c) derivatives(0.02mole) and furan-2-carboxaldehyde(0.02mol) in ethanol in presence of sodium Ethoxide was heated under reflux for 10hr. on water bath and solvent was evaporated, the resulting solid was dried in vacuum and recrystallized from absolute ethanol.

6a: 4-[(4z)-4-[2-furan)methylidene]-5-(4-hydoxy phenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazol-2-thiol: IR(KBr,cm^{-1}): 3072(aromatic C-H), 1601(C=N), 2928(Aliphatic-CH),1242(C-O-C), 1522(C=C)

6b: 4-[(4z)-4-[2-furan)methylidene]-5-(4-chloro phenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazol-2-thiol: IR(KBr,cm^{-1}): 3064(aromatic C-H), 1537(C=C), 1604(C=N), 2940(Aliphatic-CH),1220(C-O-C) ; ^{1}H-NMR δ (ppm): 7.2 (s,1H, =CH),7.4-8.2(m,1H,Ar-H), 2.5 (s, 3H,-CH3), 5.1 (s,1H,-CH-pyraz)

6C: 4-[(4z)-4-[2-furan)methylidene]-5-(4-bromo phenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-methyl-1-(4-nitro phenyl)-1H-imidazol-2-thiol: IR(KBr,cm^{-1}): 3042(aromatic C-H), 1620(C=N), 1504(Aliphatic-CH),1235(C-O-C), 1504(C=C); ^{1}H-NMR δ (ppm): 7.2 (s,1H, =CH), 5.1 (s,1H,-CH-pyraz), 7.4-8.2(m,1H,Ar-H), 2.5 (s, 3H,-CH3)

Table 1: physical properties data of the compounds synthesized in this study

Compound No.	Molecular Formula	M.P ^{0}C	Yeiled %	M.Wt	color
1	$C_{12}H_{11}N_3O_3S$	122-124	90%	277	Yellow
2a	$C_{19}H_{15}N_3O4S$	175-177	81%	381	Pale yellow
2b	$C_{19}H_{14}N_3O_3SCl$	195-196	72%	399.5	Brown
2c	$C_{19}H_{14}N_3O_3SBr$	202-204	65%	444	Dark brown
3a	$C_{19}H_{17}N_5O_3S$	185-187	50%	395	Light yellow
3b	$C_{19}H_{16}N_5O_2SCl$	198-200	55%	413.5	Yellow
3c	$C_{19}H_{16}N5O2SBr$	221-223	60%	458	Dark yellow
4a	$C_{26}H_{21}N_5O_4S$	232-234	70%	499	Red bloody
4b	$C_{26}H_{20}N_5O_3SCl$	190-192	65%	517.5	Red
4c	$C_{26}H_{20}N_5O_3CBr$	198-200	60%	562	Dark red
5a	$C_{19}H_{16}N_4O_4S$	202-204	65%	396	Orange
5b	$C_{19}H_{15}N_4O_3SCl$	224-226	70%	414.5	Dark brown
5c	$C_{19}H_{15}N_4O_3SBr$	255-256	70%	459	Yellow crystal

6a	$C_{24}H_{18}N4O_5S$	245-247	50%	474	Brown
6b	$C_{24}H_{17}N4O_4SCl$	278-280	51%	492.5	Yellow
6c	$C_{24}H_{17}N_4O_4SBr$	221-223	60%	537	Pale yellow

Anti microbial studies

The synthesized derivatives (1-6a) were tested for their anti microbial activity against staphylococcusaureus, staphylepidermidis(gram +ve), Escherichia coli, klebsilla pneumonia(gram-ve) as well as condide fungi using the well diffusion method[20]. Dimethyl sulaoxide was run as a control and the test was performed at 10 and DMSO solvent was using with concentration 100mg/ml. Metranidazol were used as standard drugs.

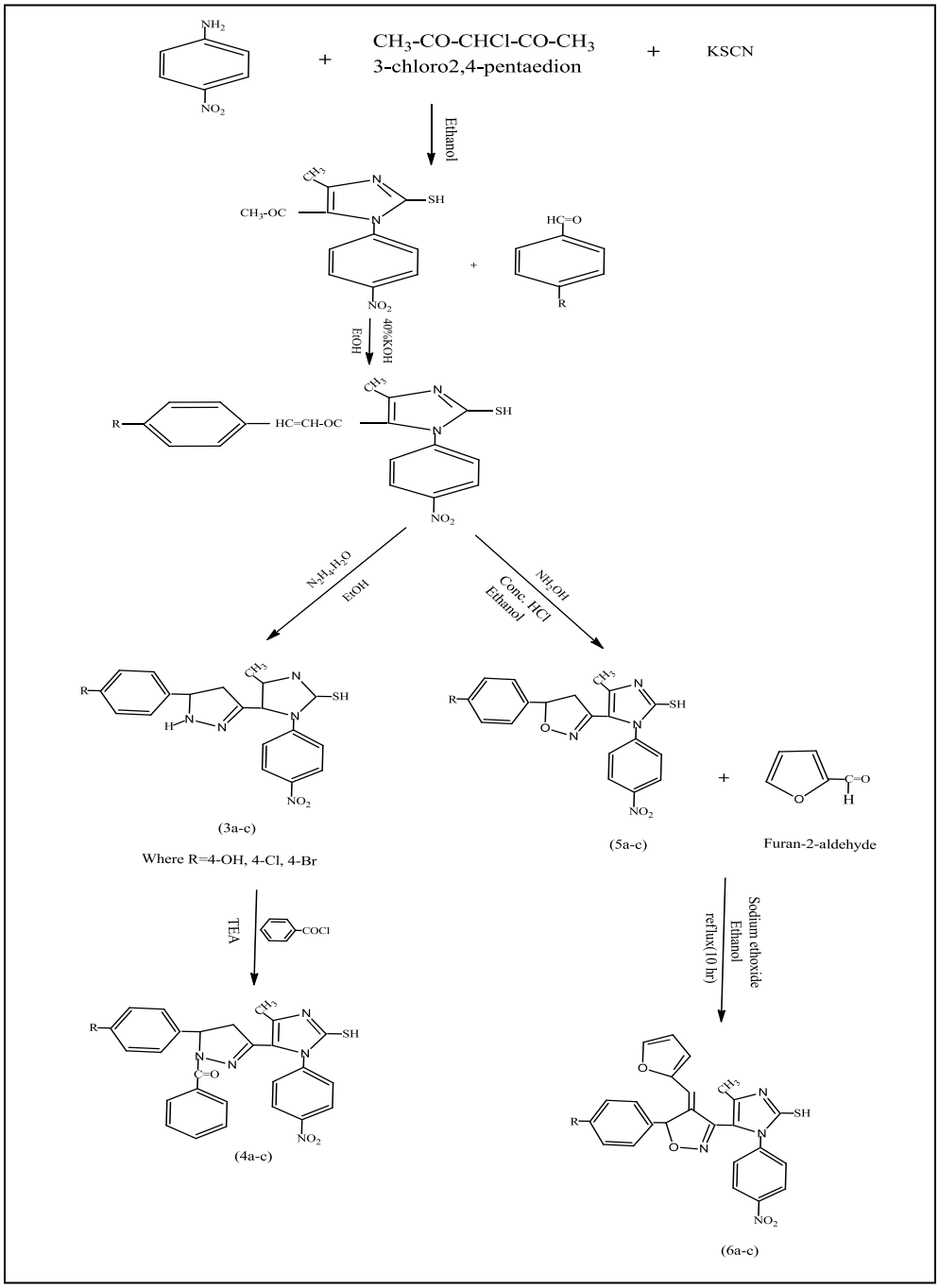
Table 2 antimicrobial activity of imidazol-2-thiol derivatives represented by% inhabitation against different microbial species.

Compound	Inhibition Zone against(in mm)				
	Gram negative		Gram positive		Fungi
	E.Coil	***Klebsiella***	***S.aureus***	***S.epidermidis***	***Condida***
1	21	14	19	14	12
2a	-	-	17	12	15
2c	11	-	18	11	17
3a	12	11	20	19	-
3b	-	14	18	12	11
4a	14	12	23	21	17
4b	11	18	21	20	18
5b	-	-	12	14	11
5c	19	12	14	12	15
6a	20	17	18	14	12
Metranidazol	21	20	22	23	20

Results and discussion

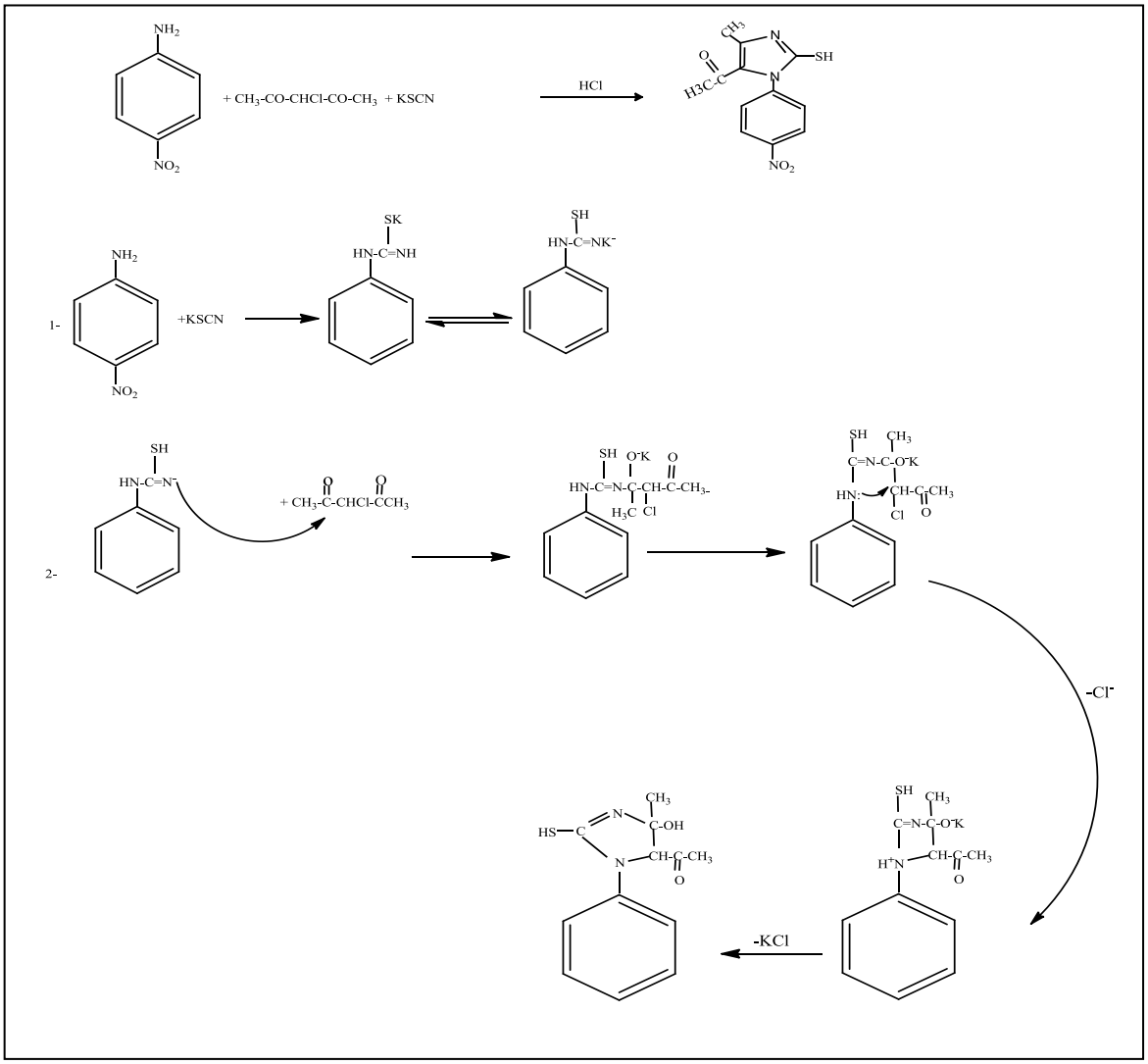
1- Synthesis

The synthetic compounds(1-6c) have been prepared according to the described processing **Scheme1**. Characterization of newly derivatives are carried out by FTIR, NMR spectra and the data is discussed in the experimental part.



Scheme1: Synthesis of imidazol derivative

The first step has been begin to convert 4-substituted aniline after treatment with 3 chloro pentandione in the presence of potassium thio cynato to imidazol derivative by cyclization. Characterized by recording their FTIR , 1HNMR spectra, the IR spectrum of compound 1 showed absorption at 1666 cm^{-1} which is due to the carbonyl stretching, while the C=N stretching frequency of imidazol ring appeared at 1539 cm^{-1}. Bands at 1595 cm^{-1} and 1475cm^{-1} related to the C=C stretching **(Fig.1)**. The ^{1}HNMR of 1 showed a doubled signal at 87.6-8.4 related to phenyl protons, the singlet appeared at δ 2.7 is due to methyl proton and δ 2.3 due to acetyl proton, while the signal at δ 12 due to SH proton **(Fig.5)**.



Scheme2: mechanism Synthesis of compound 1

Chalcones (2a-c) were synthesized in good yield from the treatment of imidazol derivative 1 with 4-substituted aromatic aldehyde in ethanol. In the FT-IR spectrum of compound 2a

(**Fig.2)**. the pyrazole ring (3a-c) were prepared by the reaction of compounds (2a-c) with excess of 80% hydrazine hydrate ethanol. The peaks at δ 10.1 and δ 4. In ^{1}H-NMR spectrum **(Fig.6)** for compound 3b. in the other hand the formation of iso oxazole ring by treatment (2a-c) derivatives with hydroxyl amine hydrochloride in acidic medium. The ^{1}H-NMR of compound 5b was shown in **(Fig 7**).

In addition, derivatives 6a-c were obtained from the reaction of furan-2-aldehyde with iso oxazole- imidazolol -2- thiol derivatives (5a-c) by refluxing for 10 hr. the structure was proved by^{1}H-NMR spectru for compound 6b shows a multiple signal to δ 7.4-8.2 due to aromatic protons and singlet at δ 5.1 related to CH-pyrazol and δ 7.2 due to (=CH) of chalcone (**Fig.8)**

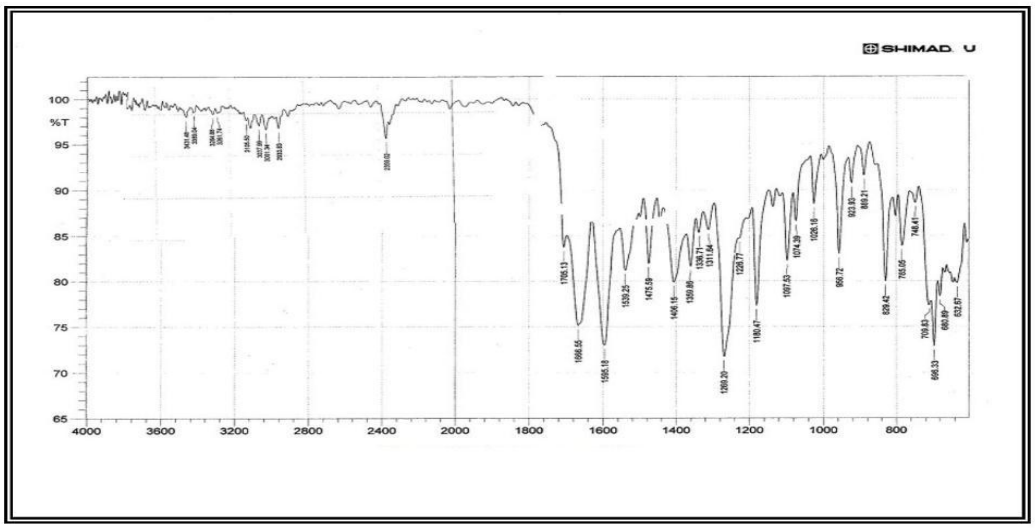


Fig. 1: FTIR for compound (1)

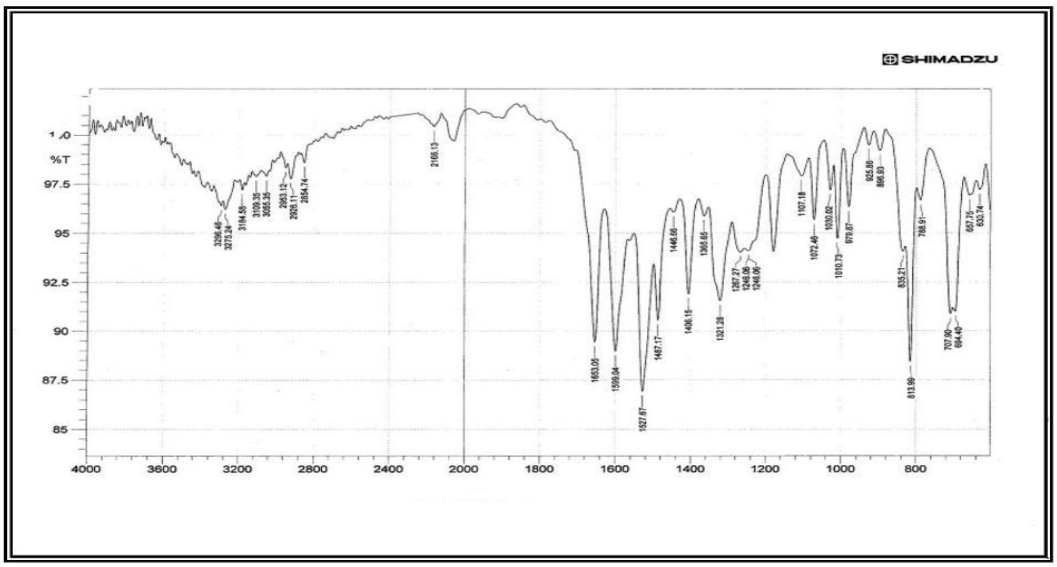


Fig. 2: FTIR for compound (2a)

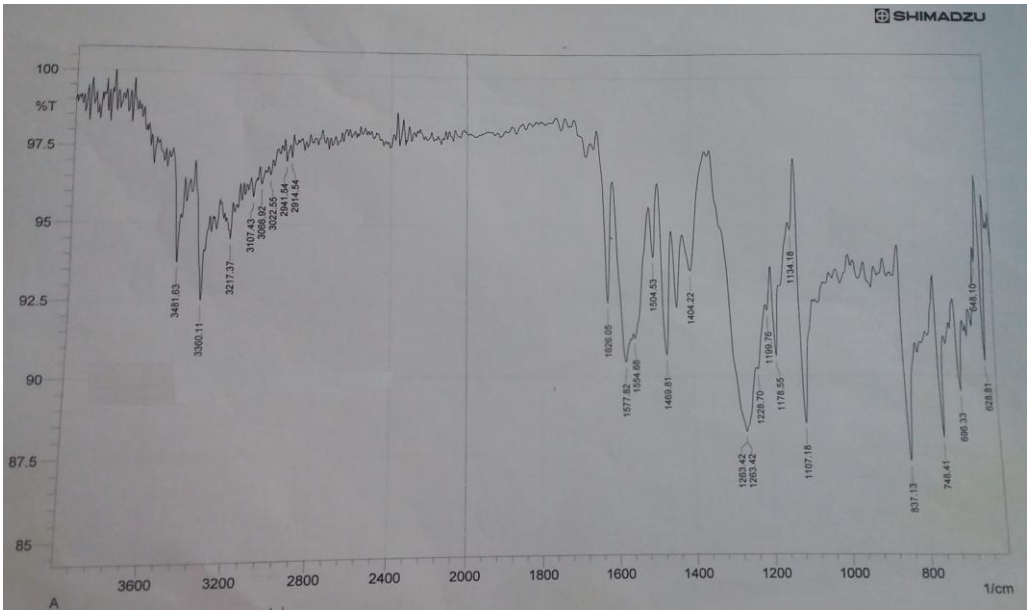


Fig. 3: FTIR for compound (4a)

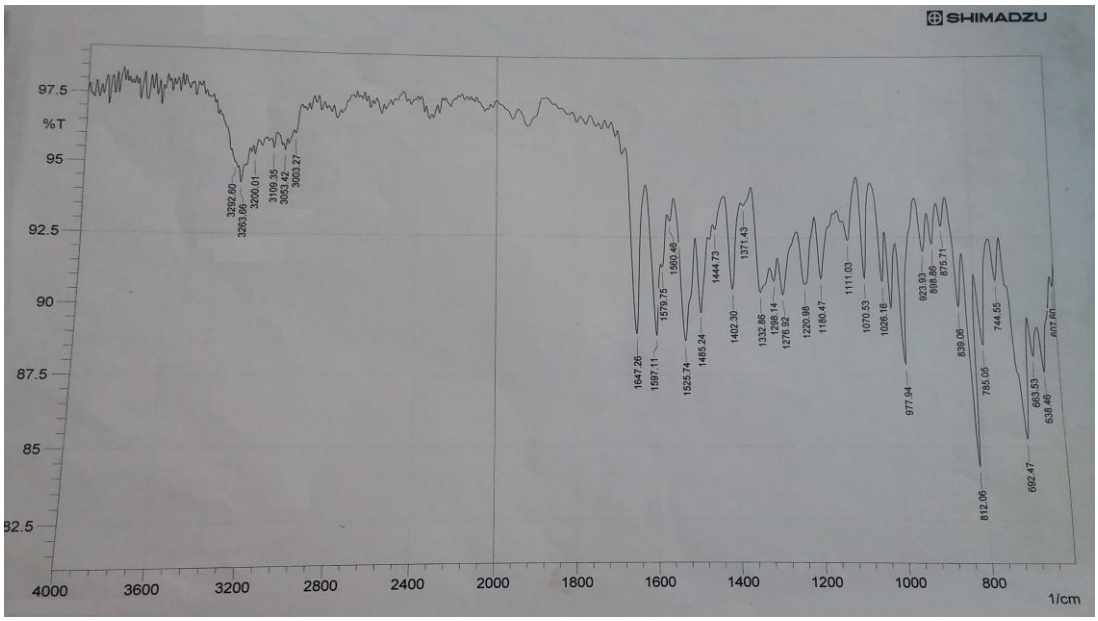


Fig. 4: FTIR for compound (3b)

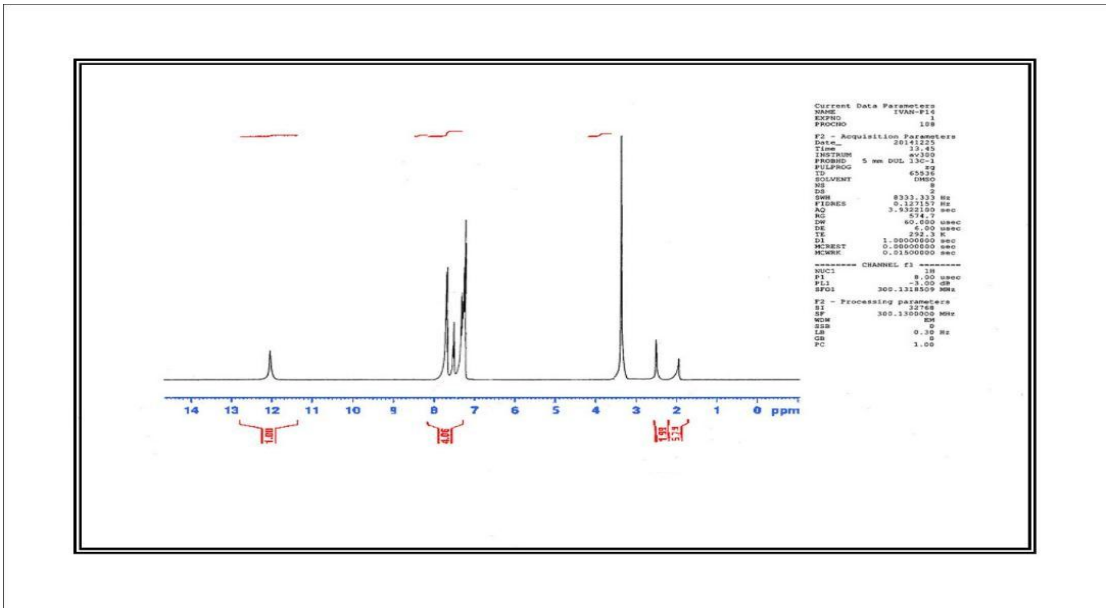


Fig. 5: ^{1}H-NMR for compound (1)

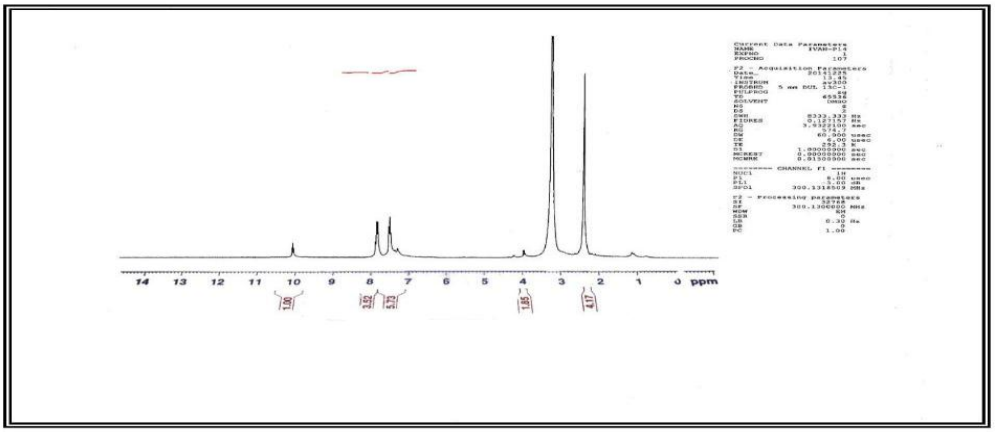


Fig. 6: ^{1}H-NMR for compound (3b)

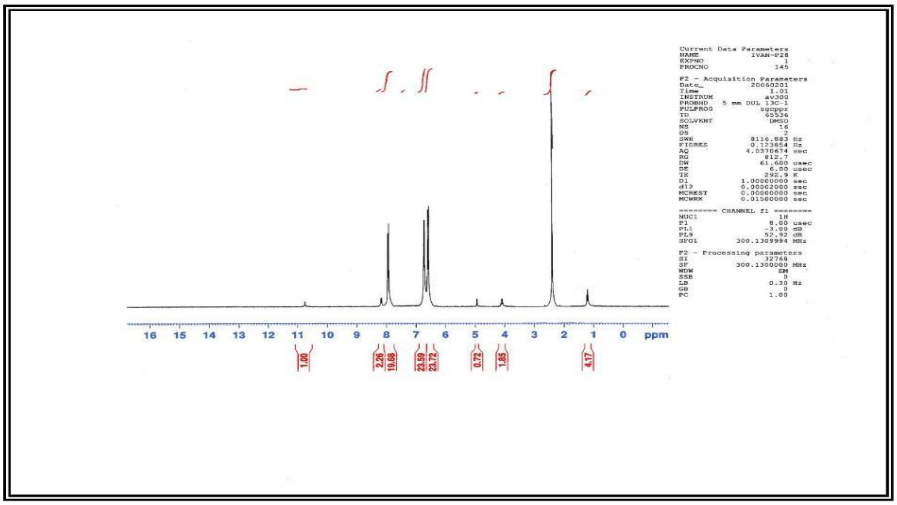


Fig. 7: ^{1}H-NMR for compound (5b)

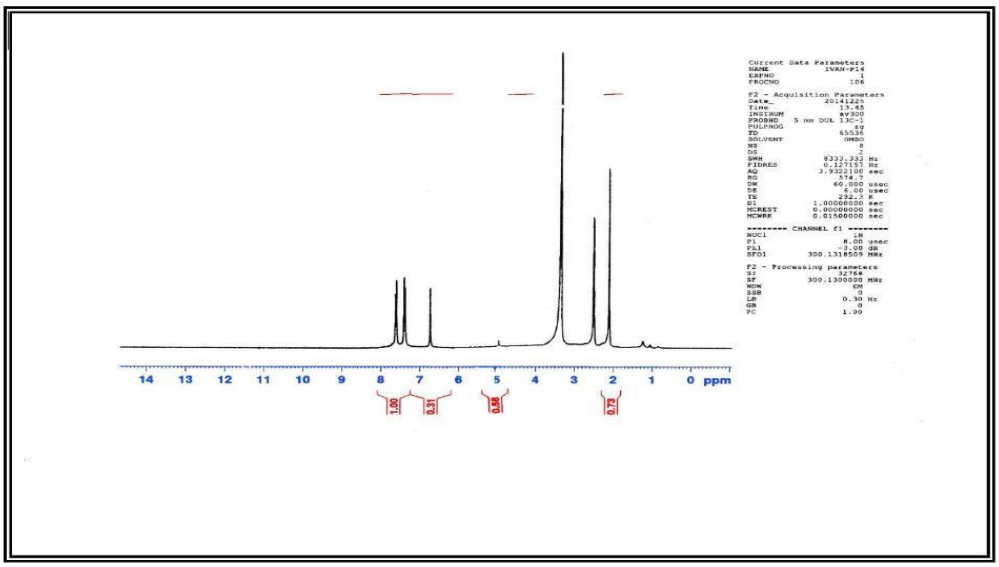


Fig. 8: ^{1}H-NMR for compound (6b)

2-Anti microbial studied

The study included the in vitro of the synthesized compounds (1-6a) against several microbial species table2 using the dilution method [21,22] . imidazole derivative 1 showed very good activity against gram- positive S.aureus bacteria and good activity against gram-negative Klebeilla bacteria and the compounds 3a, 4a, 4b show good activities against both gram positive and fungi **(Fig. 9 ,10)**

Figure 9: Activity of *E-coli strain*

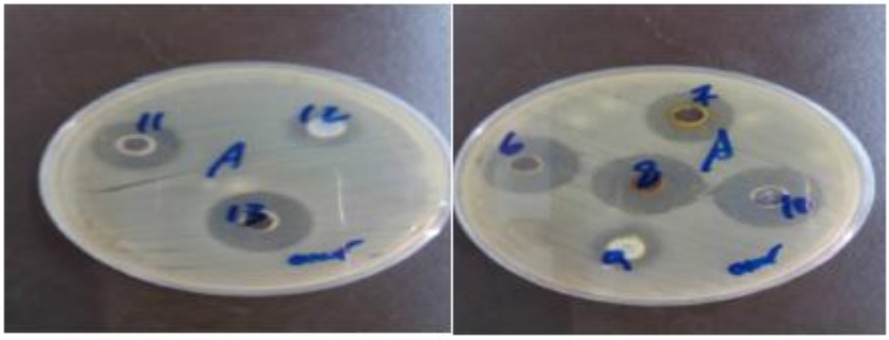


Figure 10: Activity of *Staphylococcus aureus*

Conclusions

New derivatives of imidazol-2-thiol were synthesized and characterized using FTIR,^{1}HNMR spectroscopy method. The anti microbial activity of these derivatives against some of positive and negative gram species and also against condide fungi was studied using the well diffusion method.

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